Consensus statement on the use of gonadotropin-releasing hormone analogs in children.

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PEDIATRICS

Consensus Statement on the Use of GnRH Analogs in Children

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Abstract

OBJECTIVE: Gonadotropin releasing hormone analogs (GnRHa) revolutionized the treatment of central precocious puberty (CPP). However, questions remain regarding their optimal use in CPP and other conditions. The Lawson Wilkins Pediatric Endocrine Society and The European Society for Paediatric Endocrinology convened a consensus conference to review the clinical use of GnRHa in children and adolescents.

PARTICIPANTS: When selecting the 30 participants, consideration was given to equal representation from North America (United States and Canada) and Europe, male:female ratio, and balanced spectrum of professional seniority and expertise.

EVIDENCE: Preference was given to articles written in English with long-term outcome data. The United States Public Health Grading System was used to grade evidence and rate strength of conclusions. When evidence was insufficient, conclusions were based on expert opinion.

CONSENSUS PROCESS: Participants were divided into working groups with assigned topics and specific questions. Written materials were prepared and distributed before the conference, revised based on input during the meeting, and presented to the full assembly for final review. If consensus could not be reached, conclusions were based on majority vote. All participants approved the final statement.

CONCLUSIONS: The efficacy of GnRHa to increase adult height is undisputed only in early onset (girls younger than 6 yr) CPP. Other key areas, such as the psychosocial effects of CPP and their alteration by GnRHa, need further study. Few controlled prospective studies have been performed with GnRHa in children, and many conclusions rely in part on collective expert opinion. The conference did not endorse commonly voiced concerns regarding the use of GnRHa, such as promotion of weight gain or long-term diminution of bone mineral density. Use of GnRHa in conditions other than CPP requires further investigation and cannot be suggested routinely.

Introduction

Gonadotropin releasing hormone analogs (GnRHa) are standard of care for treatment of central precocious puberty (CPP). However, despite a favorable record of safety and efficacy, significant questions remain regarding their use. The European Society for Paediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society convened a consensus conference to examine GnRHa therapy in pediatric patients. This conference did not address whether historically defined normal ages for the onset of puberty should be modified but used the operational definition of *precocious puberty* as puberty beginning prior to age 8 yr in girls and 9 yr in boys.

Methods

Participant Selection. Consideration was given to equal representation from North America (United States and Canada) and Europe; male:female ratio; and balanced spectrum of professional seniority and expertise.

Process. Thirty participants were divided into 6 groups with assigned topics and designated chairpersons. Each participant prepared a summary of the literature regarding a question that was distributed prior to the conference (held over 3 days in November, 2007). Each group revised the summaries and presented them to the full conference. If consensus could not be reached, conclusions were made based on a vote of all participants. This report is organized around the questions that were addressed, has been approved by the participants, and endorsed by LWPES and ESPE.

Evaluation of Evidence. Preference was given to articles written in English with long-term outcome data published between 1990 and 2007. The United States Public Health Grading System(1) was used to grade the evidence and strength of recommendations (Quality of evidence: I, data from ≥ 1 properly randomized controlled trial; II, from other clinical studies; III, from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees. Strength of recommendation: A, good evidence to support use; B, moderate evidence to support use; C, poor evidence to support recommendation; D, moderate evidence against use; E, strong evidence against use). Grading was reviewed by the full conference under the guidance of a methodologist/biostatistician. This report is a not a practice guideline; nonetheless, we aimed to adhere to modified AGREE criteria(2).

Section I: Initiation of GnRHa therapy for CPP

Clinical criteria

The most important clinical criteria for GnRHa treatment is documented progression of pubertal development. This is based on the recognition that many patients with CPP have a slowly or non-progressive form and achieve adult height (AH) within their target range without GnRHa(3-7). Accelerated growth velocity and skeletal maturation are other features of sustained and/or rapidly progressing CPP(8). However some patients with slowly progressive CPP and advanced bone age (BA) reach normal AH without intervention(3).

Conclusions. Progressive pubertal development and growth acceleration should be documented over a 3-6 month period prior to GnRHa therapy. This observational period may not be necessary if the child is ≥Tanner stage III (breast), particularly with advanced skeletal maturation (***CIII***).

Chronological age (CA) and psychosocial criteria

Common reasons for GnRHa therapy are potential for compromise in adult stature, inability to adapt oneself to menarche, and psychosocial difficulties. Most of the evidence concerns height outcomes (predicted versus actual AH) and age at initiation of therapy, but no randomized controlled trials quantifying the effect of therapy on AH are available. The Bayley-Pinneau method is commonly used to predict AH and is likely better than other prediction methods(9); however, in some instances, it may over predict height by several centimeters(10,11).

The greatest height gain is observed in girls with onset of puberty under 6 years [average gain 9-10 cm, but with variation among studies(6,12-16)]. Girls with onset between 6 and 8 years comprise a heterogeneous group that may have a moderate benefit ranging from 4.5 ± 5.8(13) to 7.2 ± 5.3 cm(6). Insufficient data exist to relate chronologic age to height outcomes among boys(17).

Data regarding the psychosocial impact of untreated or treated CPP are inconclusive and whether delaying puberty with GnRHa may improve social functioning is still an open question. Early menarche in the general population is associated with risk-taking behavior(18), but it is unclear whether such data can be generalized to CPP. In patients with severe developmental delay, CPP may be associated with inappropriate behavior. If suppression of menses is the primary goal, GnRHa is only one of several therapeutic options, including progestogens that could be considered(19).

Conclusions. Girls with onset of progressive CPP before age 6 years benefit most in terms of height from GnRHa. The decision to initiate therapy in girls with onset *after* age 6 should be individualized (***BII***). Treatment should be considered in all boys with onset of progressive CPP before 9 years who have compromised height potential (***CIII***). The use of GnRHa solely to influence the psychosocial consequences of CPP or to delay menarche should be considered carefully given the absence of convincing data (***CIII***). Further studies evaluating the effects of GnRHa therapy on quality of life and psychosocial functioning are needed.

Adopted children

Boys and girls adopted internationally are at risk of CPP, although data are limited in boys(20,21). Response to GnRHa in adopted girls with precocious or early normal puberty appears comparable to that seen in non-adopted girls(22). Adopted children may be at increased risk of emotional and behavioral problems(23), but no data are available to demonstrate that GnRHa therapy improves psychological wellbeing(24).

Conclusions. Although international adoption constitutes a risk factor for CPP, adopted children should be treated no differently than non-adopted children with CPP (***CIII***).

Hormonal criteria

LH measurements are the most valuable biochemical parameter for the diagnosis of CPP. As

prepubertal LH levels are <0.1 IU/L , LH assays used should have a detection limit near 0.1 IU/L(25-27). In one study of normal children, basal LH levels distinguished prepubertal (LH <0.2 IU/L) and pubertal males with 100% sensitivity and specificity but 50% of girls with Tanner stage 2 breasts had levels in the prepubertal range(27).

LH can be measured after stimulation with GnRH (single serum sample at 30-40 min (27-29)) or with a GnRHa, such as aqueous leuprolide (single sample at 60 min(30,31)). Peak LH values show an overlap between prepubertal and early pubertal children. As with basal LH, variability among assays and paucity of normative data hamper the development of diagnostic cut-offs for CPP although an (assay-specific) prepubertal limit of peak LH of 3.3 to 5.0 IU/L has been suggested(25,27,28).

LH levels provide more information than FSH. However, the stimulated LH/FSH ratio may help differentiate progressive CPP, which tends to have higher LH/FSH ratios, from non progressive variants that do not require GnRHa therapy(32-34).

For estradiol, the most sensitive measurements (tandem mass spectrometry, MS) have shown that prepubertal levels may be <1 pg/ml (3.7 pmol/L) and undetectable with commonly available assays(35). Thus, in non MS assays, measurable estradiol only confirms relatively advanced puberty. Similarly, testosterone assays with detection limits >10 ng/dL may not discriminate prepubertal from early pubertal levels(36) . For estradiol and testosterone, the laboratory used must have a defined prepubertal range.

Conclusions. Sensitive assays with pediatric norms should be used and stimulation results interpreted depending on agent used **(*BII*)**. The same caveats are important if hormonal testing is used to monitor therapy (see below). Basal LH levels are useful screening tests and may be diagnostic (***BII***). Stimulated LH levels are important but interpretation suffers from assay variability and absence of clear diagnostic cutoffs (***BII***). Gonadal sex steroid levels can add information in support of the diagnosis but are not sufficient (***BII***).

Pelvic ultrasound

Patients with CPP have increased ovarian and uterine dimensions compared to prepubertal controls and girls with premature thelarche(37). For CPP, cutoff values for uterine length range from 3.4 to 4.0 cm. The presence of an endometrial echo is highly specific (~100%) but less sensitive (42 to 87%)(34). The cutoffs for a pubertal ovarian volume range between 1-3 ml (volume = length x width x height x 0.5233)(38).

Conclusions. Pelvic ultrasound is helpful in differentiating CPP from premature thelarche as and adjunct to GnRH stimulation (***BII***).

CNS imaging

CPP may be a sign of CNS pathology. Unsuspected intracranial pathology has been reported in 8% of girls(39,40) and 40% of boys(41) without neurological findings or neurofibromatosis. The percentage of children with unsuspected intracranial pathology decreases with age(39-41). Only 2-7% of girls who have onset of CPP between 6 and 8 years of age have unsuspected pathology, and only about 1% have a tumor such as a glioma or astrocytoma(39,40). Factors that may decrease the likelihood of finding a tumor include racial/ethnic background, family history of CPP, and adoption.

Conclusions. All boys with CPP and girls with CPP at less than 6 years of age should have a head MRI. It is controversial whether all girls who develop CPP between 6-8 years of age require head MRIs. Girls with neurological findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination (***BII***).

Section II: Available GnRHa and therapeutic regimens for CPP

Currently available therapeutic regimens

All available GnRHa are effective despite different routes of administration, dosing, and duration of action (Tables 1, 2 and 3)(42,43). The depot preparations are preferred because of

improved compliance (44-46). In most children, monthly injections adequately suppress the gonadotropic axis, but some children require more frequent injections or higher than standard doses. The 3 month formulations are comparable to monthly dosing, but no randomized comparative trial is available(42,47-49). In one prospective trial, 7.5 mg leuprolide monthly suppressed LH more effectively than 11.25 mg three-monthly, although sex steroid concentrations were equally inhibited(50). The 50 mg histrelin acetate implant provides sustained suppression for 12 months(51,52).

Conclusions. A variety of GnRHa formulations are available and efficacious. The choice of a particular agent depends on patient and physician preference (***CIII***).

Treatment monitoring

Progression of breast or testicular development is suggestive of treatment failure(52-56), but progression of pubic hair may indicate normal adrenarche. Growth velocity, height SDS and BA advancement should decline during treatment. Vaginal bleeding may occur after the first adminstration of GnRHa, but subsequent bleeding suggests lack of efficacy or incorrect diagnosis. Markedly decreased growth velocity (≤-2 SDS) or rapid BA advancement should also prompt re-assessment. BA can be used to update AH prediction understanding that the Bayley-Pinneau method may overestimate AH(57). If elevated, random LH levels using an ultrasensitive assay, indicate lack of suppression. Stimluated LH values (using GnRH, acqueous GnRHa, or the free GnRHa contained in depot preparations) can also be used to assess effectiveness. FSH levels are not usually used to monitor suppression. If measured, testosterone and estradiol levels should be in a prepubertal range for the assay used(44,51,53-56,58). No long-term data provide compelling support for any specific short-term monitoring scheme.

Conclusions. GnRHa injection dates should be recorded and adherence with dosing interval monitored (***BII***). Tanner stage and growth should be assessed every 3-6 months, and BA monitored

periodically (***BII***). There was no consensus about the routine use of random or stimulated measurements of gonadotropins or sex steroids for monitoring therapy. In patients with suboptimal clinical response, there was consensus about need for comprehensive reassessment (***CIII***). Additional information on the relationship between on-treatment measures of gonadotropic axis suppression and outcomes are needed.

Adverse events

GnRHa are generally well tolerated in children and adolescents. Systemic complaints, such as headaches or hot flashes occur occasionally but are usually short-term and do not interfere with therapy. Local adverse events occur in about 10-15% of patients and necessitate a change in agent when persistent because they can result in sterile abscesses in a fraction of the patients(54,55,59). Although exceedingly rare, anaphylaxis has been described.

Potential new therapeutic agents for the treatment of CPP

GnRH *antagonists* cause immediate and direct inhibition at the level of pituitary GnRH receptors(60). Theoretical advantages over GnRHa include eliminating the initial "flare" in gonadotropic axis activation as well as rapid recovery of suppression once therapy is withdrawn. Depot and non-peptide orally active GnRH antagonists are under development(61), and could be evaluated in children with CPP in the future.

Therapeutic agents that can be combined with GnRHa for the treatment of CPP

Adjunctive therapies that may improve outcomes (AH, for example) of GnRHa therapy include pure or selective E2 receptor blockers, aromatase inhibitors (62), pure anti-androgens, sex steroids(63) or non-aromatizable anabolic steroids(64). The addition of oxandrolone increased AH compared to GnRHa alone in a small non randomized study (n=10)(64). The addition of growth hormone (GH) increased AH compared to GnRHa alone in girls with CPP and slow growth velocity in small (n=10

and =17), non randomized series (65,66). The addition of GH increased height outcome in a randomized controlled study (n=46) in adopted girls with precocious or early puberty (22). However, no large scale randomized controlled trials evaluating the addition of GH to GnRHa in CPP have been performed.

Conclusions. The addition of GH or oxandrolone to GnRHa cannot be routinely recommended. These adjunctive therapies require validation by larger studies with consideration of potential side effects (***CIII***).

Section III. Discontinuation of GnRHa therapy in CPP

Factors that could influence the decision to stop GnRHa treatment depend on the primary goal(s) of therapy including maximizing height, synchronizing puberty with peers, ameliorating psychological distress, and facilitating care of the developmentally delayed child. Available data only permit analysis of factors that impact AH among girls.

Treatment duration. Several studies have reported a direct relationship between treatment duration and AH(14,15,67-69) and an inverse relationship between age at pubertal onset or at initiation of therapy and AH(6,14,67-69). However, deciphering the respective influences of age at onset of puberty, age at initiation of therapy and treatment duration is problematic since these variables are interrelated. Undue delay in initiation of therapy (more than 1-2 years) may compromise AH.

Parent/patient preference, anticipated time of menarche, CA and BA. In studies examined, the wishes of the patient and family and the physician's decision were stated as deciding factors for cessation of treatment (13,15,68,70-73). The mean age at treatment discontinuation ranged from 10.6 to 11.6 yr with mean BA ranging from 12.1 to 13.9 yr, and mean age at menarche of ≈12.3 yr. Discontinuation at CA≈11.0 yr(13) and BA≈12.0 yr(14,67) has been associated with maximum AH. However BA is not an appropriate single variable because a BA ≈12.0 yr can be observed at different

CAs and because BA is unreliable to predict height gain after treatment(12-15,72). One study has suggested that height gain after treatment may be higher in those with early (<6 yr) vs late treatment (6).

Height and growth velocity. Although growth velocity during therapy(6,13-15,67-69,71,72) and height at interruption of therapy are positively associated with AH(6,13,14), they cannot be used as independent factors for deciding when to stop treatment. In a child with unexplained marked deceleration of growth, consideration might be given to stopping treatment or to introducing adjunct therapies.

Conclusions. There is insufficient evidence to rely on any *one* clinical variable (CA, duration of therapy, BA, height, target height, growth velocity) to make the decision to discontinue treatment (***CIII***). It is, therefore, reasonable to consider these parameters and informed parent and patient preferences, with the goal of menarche occurring near the population norms (***CIII***).

Section IV. Outcomes of GnRHa therapy for CPP

Reproductive function

In girls, follow-up studies have been performed in late teens(68,69,74-76) and up to 31 yr in one study(77) and have reported that ovarian function was not impaired(68,69,74,75,78,79). Menses began 2 to 61 months (mean ≈16 month) after end of treatment(69,74-77). Regular ovarian cycles occurred in 60% to 96% of the patients, without differences from reference populations(69,74-77). Infertility has not been reported. Of 28 reported pregnancies(69,74,75,77), 7 were terminated and 21 resulted in healthy children(69,75,77). In boys, three small studies showed no differences from controls in gonadal function at the age of 15 to 18 years (68,78,79). Paternity rates have not been reported.

Conclusions. The available data suggest that gonadal function is not impaired in girls treated

with GnRHa (***BII***). Nevertheless, available data are limited. Long-term data on fecundity and ovarian reserve of treated patients with CPP are needed.

BMI and correlates of metabolic syndrome

Childhood obesity is associated with earlier pubertal development in girls and early sexual maturation is associated with increased prevalence of overweight and obesity. There has been concern that GnRHa therapy may affect BMI. Eleven studies address BMI outcome in girls with CPP(6,12,49,69,75,80-85), 2 include boys(78,80) and 1 includes girls with early puberty (onset at age 8 and 9 yr)(86). Before GnRHa treatment, mean BMI SDS was above average in girls with CPP in all studies, while results were split in males(78,80). The combined analysis indicates that BMI SDS did not increase on treatment irrespective of age at presentation. At AH, mean BMI SDS ranged from 0.1 to 1.7, with an overall slight decrease from pretreatment BMI. No reports regarding metabolic syndrome and GnRHa treatment were identified.

Conclusions. Above average BMI is frequent at diagnosis of CPP. Long-term GnRHa treatment does not appear to cause or aggravate obesity, as judged from BMI (***BII***). Studies of body composition and fat distribution are needed.

Bone mineral density (BMD)

BMD may decrease during GnRHa therapy. However, subsequent bone mass accrual is preserved and peak bone mass does not seem to be negatively affected by treatment(12,82,87). There is some suggestion that discontinuation of treatment in girls with a BA ≤11.5 yr may lead to greater BMD(87) and that, as in all adolescents, optimum calcium and vitamin D intake may positively influence bone mass(82).

Conclusion. Young adults treated with GnRHa for CPP in childhood ultimately accrue BMD within the normal range for age (***BII***).

Risk of polycystic ovarian syndrome (PCOS)

The possibility that CPP is a first manifestation of PCOS has been raised(88). PCOS occurred in 0-12% of girls with CPP followed prospectively (12,89-91), as compared to 5-10% in the general population(92). Single studies have reported i) an increased average ovarian size following CPP due to hypothalamic hamartoma(75) ii) a higher prevalence of exaggerated adrenarche in CPP than in controls(93) and iii) the occurrence of signs of PCOS 0.5-4.0 years post-menarche(94).

Conclusions. Follow-up of treated or untreated girls with CPP into the mid-teens suggests that the development of PCOS (***BII***) or polycystic ovary morphology (***CIII***) is not clearly different from that in the general population. Premature adrenarche and early childhood insulin resistance are potential risk factors for PCOS but it is not clear if the presence of these conditions along with CPP increases the eventual risk of PCOS (***CIII***). Longitudinal data through adolescence are needed.

Section V. Psychosocial development

Potential psychological consequences of CPP, including risk for emotional distress and problem behavior, are often used to justify treatment with GnRHa(95,96). Hormonally-induced behavioral changes (e.g., in aggression, sexuality) that occur during normal puberty(97) may occur earlier in children with CPP, perhaps consistent with the hormonal effects on brain development observed in rodents(98).

Limited data are available regarding psychological consequences of CPP, and the few existing studies have limitations that have yielded inconsistent conclusions(99). In 2 studies examining psychological functioning in girls with CPP before and after treatment(24,100), no consistent patterns of change were observed. GnRHa have been suggested to adversely affect mood and cognition in adults (101) but similar effects have not been evaluated in children.

Conclusions. There is little evidence to show whether CPP leads to psychological or

behavioral problems or whether treatment with GnRHa is associated with improved psychological outcome (***CIII)***. Thus, no recommendations are possible related to psychosocial outcomes. Controlled studies with standardized instruments are needed.

Section VI. Use of GnRHa in conditions other than CPP

Gonadal protection in children undergoing chemotherapy

Infertility represents one of the main long-term consequences of chemotherapy. Studies evaluating the effects of ovarian suppression by GnRHa during chemotherapy in adult and adolescent patients have yielded inconsistent results(102-104). A prospective, randomized trial in adult women is ongoing.

Conclusions. Routine use of GnRHa for gonadal protection in children undergoing chemotherapy cannot be suggested (***CIII***).

Increasing AH of children with idiopathic short stature (ISS)

The effect of GnRHa therapy on AH has been evaluated in girls with ISS and normal puberty (8-10 yrs of age) with a mean gain compared to predicted height of 0 to 4.2 cm(6,14,15,57,69,71,73,105-110). In boys with rapidly progressing puberty, GnRHa therapy increased AH compared to predicted height(5). The effects of combined GH and GnRHa therapy in children with ISS are controversial(111) with mean gains of 4.4 to 10 cm with combination therapy *vs* -0.5 to 6.1 cm in untreated controls(112,113). In these studies, one cannot definitively separate the effects of GH from GnRHa. In two randomized studies in adopted girls with normal puberty, GnRHa plus GH was compared with GnRHa alone with a 3 cm height gain with combination therapy(22,114). Disadvantages of the use of GnRHa in children with ISS include: absence of pubertal growth acceleration, delayed puberty with potential psychosocial disadvantage, and decreased bone mineral density. Long-term follow-up studies are lacking.

Conclusions. GnRHa therapy alone in children with ISS and normally timed puberty is minimally effective in increasing AH, may compromise bone mineral density and cannot be suggested for routine use (***DII***). Combined GnRHa and GH therapy leads to a significant height gain, but may have adverse effects. Routine use of GnRHa in children with ISS being treated with GH cannot be suggested (***CIII***).

Increasing AH of children born small for gestational age (SGA)

Short children born SGA usually have a normal pubertal timing although some of them have rapidly progressing puberty, and may be treated with GH(92,115). Data on the additional effect of GnRHa are limited(113).

Conclusion. Routine use of the combination of GnRHa and GH in children born SGA cannot be suggested (***CIII***).

Increasing AH of children with severe hypothyroidism

Some children with severe hypothyroidism are at risk for rapid progression through puberty and diminished AH. In the only study available, combined GnRHa and LT4 and LT4 alone produced similar gains in height SDS (116).

Conclusions. Routine use of combined therapy with GnRH and LT4 cannot be suggested (***CIII***).

Increasing AH of children with growth hormone deficiency (GHD)

Some children with GH deficiency are short at the start of puberty and at risk for short adult stature. Retrospective studies evaluating the addition of GnRHa to GH involve limited number of subjects and provide controversial results(117-119). Three prospective studies reporting near-adult or AH have shown approximately a 1 SD height gain(120-122), possibly without detrimental effect on BMD(123) .

Conclusions. Routine use of combined therapy with GnRH and GH in GH deficient children with low predicted AH at onset of puberty cannot be suggested (***CIII***).

Increasing AH of children with congenital adrenal hyperplasia (CAH)

One nonrandomized study examined the effect of combined GH and GnRHa treatment on AH in 14 children with CAH and normal or precocious puberty and found a 1 SD increase in AH in comparison with standard treatment for CAH(124).

Conclusions. Further studies are needed to determine whether GnRHa therapy alone or in combination with GH should be used in children with CAH and low predicted AH. Routine use of GnRHa in CAH cannot be suggested (***CIII***).

Children with autism

Despite one controversial manuscript reporting that GnRHa may benefit behavioral symptoms in children with autism(125), the consensus is that there is no current evidence for GnRHa therapy for this indication (***CIII***).

Summary

Several important observations emerged from this conference. Despite a considerable body of literature on the use of GnRHa, few rigorously conducted and controlled prospective studies are available from which to derive evidence-based recommendations. Most of our conclusions are categorized as ***CIII***, a level of evidence that underscores the need for further research in key areas, such as the psychosocial effects of GnRHa treatment for CPP. The efficacy to increase AH is undisputed only in early onset progressive CPP. This highlights the need to increase our knowledge of the pathophysiology and normal limits of puberty and of the physical and psychosocial consequences of treated and untreated CPP. The conference's systematic review also highlighted the lack of objective support for commonly voiced concerns such as the propensity for GnRHa to promote weight gain or to

lead to long term diminution of bone mineral density. Use of GnRHa in conditions other than CPP requires further investigation and cannot be routinely suggested.

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Table 1. Characteristics of GnRHa

	Rapid-acting	Monthly depot	3-month depot	12 month implant
Dosing	3-4 times daily (intranasal) or every day (subcutaneous)	every 28 days	every 90 days	every year
Peak serum concentrations	10-45 min	4 hrs	4-8 hrs	1 month
Onset of therapeutic suppression	2-4 weeks	1 month	1 month	1 month
Advantage	Quick on/off	Dosing and efficacy well studied	Fewer injections and fewer compliance concerns	No injections needed
Disadvantage	Multiple daily doses needed / compliance very difficult	Painful injections / suboptimal compliance	Painful injection	Requires surgical procedure for insertion and removal

Table 2. Rapid-acting formulations of GnRHa

GnRH analog	Administration	Starting Dose
Nafarelin	Nasal spray	800 µg BID
Buserelin	Nasal spray	20-40 µg/kg/day
Buserelin	Subcutaneous	1200-1800 µg/day
Leuprolide	Subcutaneous	50 µg/kg/day
Deslorelin	Subcutaneous	4-8 µg/kg/day
Histrelin	Subcutaneous	8-10 µg/kg/day
Triptorelin	Subcutaneous	20-40 µg/kg/day

Table 3: Depot GnRHa formuations(42,47,48)

Depot preps	Brand name	Starting Dose
Goserelin	Zoladex LA	3.6 mg every mo OR 10.8 mg every 3 mo
Buserelin	Suprefact depot	6.3 mg every 2 mo
Leuprolide	Enantone or Lupron-depot	3.75 mg every mo/ OR 11.25 mg every 3 mo
	Prostap SR	4-8 µg/kg/day
	Lupron-depot-PED	7.5, 11.25, or 15 mg every mo (0.2 to 0.3 mg/kg/mo) OR 11.25 mg every 3 mo*
Triptorelin	Decapeptyl, Gonapeptyl	3 or 3.75 mg every mo OR 11.25 mg every 3 mo
Histrelin	Supprelin LA	50 mg implant every year

no data is available on the use of the 22.5 mg 3 mo depot in children

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